REMARKS

Claims 112-118, 120, 123, 124, 127, 131-134, 137-139, 141-145, 147-153, 157, 158, 161, 165-168, 171-173, 175-178, 180-190, 192, 196, 197, 200, 204, 205, 210-212, 214-217, and 219-226 are pending. Claims 1 – 111, 119, 121, 122, 125, 126, 128-130, 135, 140, 146, 154-160, 162-164, 169, 170, 174, 179, 191, 193-195, 198, 199, 201-203, 208, 209, 213, and 218 have been cancelled. Claim 149 has been amended. No new matter has been added.

Applicants reserve the right to pursue the claims as originally filed in one or more continuing applications.

Claim Rejections 35 § USC 101

The Examiner has rejected claims 149-153, 157, 158, 161, 165-168, 171-173, 176-178, 180 and 181 under 35 USC § 101 as being, allegedly, directed to non-statutory subject matter.

The Examiner argues that "the claims encompass embodiments wherein the electronic and magnietic media encompass signal and carrier wave embodiments wherein the electronic and magnetic media encompass signal carrier wave embodiments that are also not statutory subject matter." (Office Action, p.3).

In the interest of expediting prosecution, and in no way acquiescing to the validity of the Examiner's rejection, Applicants have amended the claims to be more clearly define what is being claimed.

Accordingly, Applicants respectfully request that the rejection be withdrawn.

Claim Rejections 35 USC § 103(a)

The Examiner has rejected claims 112-117, 123, 124, 127, 131-134, 137-139, 141, 143-145, 147-148, and 221-224 under 35 U.S.C. §103(a) as being unpatentable over Petricoin (The Lancet, 359:572 – 577, 2002), in view of Golub et al. (Science, 286:531-537, 1999).

The Examiner has also rejected claims 112-118, 120, 123, 124, 127, 131-134, 137-139, 141-145, 147-153, 157, 158, 161, 165-168, 171-173, 175-178, 180-190, 192, 196, 197, 200, 204, 205, 210-212, 214-217 and 219-224 under 35 U.S.C. §103(a) as being unpatentable over Petricoin in view of Golub, as applied to claims 112-117, 123, 124, 127, 131-134, 137-139, 141, 143-145, 147-148, and 221-224, above, and further in view of Barnhill, U.S. Patent No. 6,789,069 (the '069 reference herein).

For the sake of brevity, the two rejections under 103(a) are addressed together because each rejection relies on the Petricoin in combination with a secondary reference.

Applicants respectfully traverse these two rejections.

The present claims are directed to performing multivariate analysis on a first set of samples that includes samples classified into at least two different biological states and, separately, performing multivariate analysis on a second set of samples that includes samples classified into the different biological states. The method further requires the **selection of first and second subsets of qualified common data elements from the first and second data sets, respectively, and further selecting an intersection subset of data elements from these two subsets**.

The Examiner argues that "Petricoin discloses analyzing two biological state classes- 'unaffected' and 'affected' wherein the affected group is known to have cancer (and) discloses analyzing two independent sets of samples." (Office Action, p.5). The Examiner argues that "the original test data is analysis of 'the first set' of samples (and) (a) second 'sample set' is composed of 50 control samples for the masked analysis, other unaffected samples and benign disease control samples (and) results from the test (masked data) may be added to the model/dataset to improve prediction." (Office Action, p.5). The Examiner contends that "Petrocoin discloses that both 'samples' were collected and separately statistically analyzed to classify samples into different biological states AND also discloses an 'intersection' subset (the totality of the data used for classification after 'improvement.')." (Office Action, p.5). The Examiner argues

that "the results obtained from two independent samples (preliminary and masked) were 'intersected' wherein data elements in the intersection subset is a member of both subsets." (Office Action, p.5).

The Examiner admits that the Petrocoin reference "does not teach selecting a second subset and displaying the intersection subset." (Office Action, p.7).

The Examiner argues that "Golub discloses a method for classifying cancer by using gene expression monitoring (and) discloses using two classes (ALL and AML) and two samples comprising both classes." (Office Action, p.7). The Examiner argues that "Golub discloses selecting 'predictors' from the first sample and testing the predictors on an independent 34 leukemia samples...(and) further discloses prediction strengths for both the initial (cross-validation) sample and an independent sample and selection of data elements with high prediction strength for both samples (selecting a first and a second subset)." (Office Action, p.7). The Examiner contends that "Golub discloses displaying the intersection (fig. 3)." (Office Action, p.7).

The Examiner argues that "it would have been obvious to one skilled in the art at the time the invention was filed to modify the method of Petrocoin to select both a first and a second subset of data elements and display the intersection, as taught by Golub, where the motivation would have been to test a model/hypothesis and to compare the results, as taught by Golub." (Office Action, p.8).

Applicants submit that the combination of references does not teach or suggest the invention as claimed. Nowhere does the Petrocoin reference teach or suggest the **selection of subsets from the first and second data sets**. None of the Golub or Barnhill references cures the defects of the Petrocoin reference. None of the references, alone or in combination, teaches or suggests **the selection of an intersection subset from a first or second data set, and none of the references provide any motivation to use any set or subset of selected data with the expectation of selecting an intersecting subset with similar properties**.

The Examiner argues that "it is noted that applicants reiterate previous presented arguments directed toward the prior art of record in comparison to ***the exact terms recited in the instant claims***." (Office Action, p.11; emphasis provided by the Examiner). The Examiner argues further that the analysis ***for obviousness need not***

seek out precise teachings directed to the specific subject matter of a claim...(and) ***the analysis can take into account the inferences and creative steps that a person of ordinary skill in the art could employ and that a person of ordinary skill in the art is also a person of ordinary creativity***." (Office Action, p.11; emphasis provided by the Examiner).

"'[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.'" KSR, 550 U.S., 82 USPQ2d at 1396.

The Examiner has failed to support the instant rejections under 35 USC 103(a) with any reasons of why the claimed invention would have been obvious according to the standards outlined in the MPEP.

Applicants direct the Examiner to the MPEP at 2111.01, at IV. that sets forth APPLICANT MAY BE OWN LEXICOGRAPHER. The MPEP guides examination such that:

> An applicant is entitled to be his or her own lexicographer and may rebut the presumption that claim terms are to be given their ordinary and customary meaning by clearly setting forth a definition of the term that is different from its ordinary and customary meaning(s). See In re Paulsen, 30 F.3d 1475, 1480, 31 USPQ2d 1671, 1674 (Fed. Cir. 1994) (inventor may define specific terms used to describe invention, but must do so "with reasonable clarity, deliberateness, and precision" and, if done, must "'set out his uncommon definition in some manner within the patent disclosure' so as to give one of ordinary skill in the art notice of the change" in meaning) (quoting Intellicall, Inc. v. Phonometrics, Inc., 952 F.2d 1384, 1387-88, 21 USPQ2d 1383, 1386 (Fed. Cir. 1992))...
>
> ...The specification should also be relied on for more than just explicit lexicography or clear disavowal of claim scope to determine the meaning of a claim term when applicant acts as his or her own lexicographer; the meaning of a particular claim term may be defined by implication, that is, according to the usage of the term in >the< context in the specification. See Phillips v. AWH Corp., *>415 F.3d 1303<, 75 USPQ2d 1321 (Fed. Cir. 2005) (en banc); and Vitronics Corp. v.

> Conceptronic Inc., 90 F.3d 1576, 1583, 39 USPQ2d 1573, 1577 (Fed. Cir. 1996). Compare Merck & Co., Inc., v. Teva Pharms. USA, Inc., 395 F.3d 1364, 1370, 73 USPQ2d 1641, 1646 (Fed. Cir. 2005),

The present invention involves developing **at least two different data sets that have been developed independently of each other**. Each data set includes data points from a plurality of subjects. The subject data from each subject indicates a form of biological state class. Each data set has subject data from at least two subjects belonging to each of the biological state class. As taught at p. 23 of the disclosure, "the first data from a first set of samples" and the second data from a second set of samples" are independent:

> As a first step, a plurality of independent data sets is obtained. The data sets comprise data points, e.g., a label referring to a sample number or patient number, representing a plurality of samples from multiple sample sources. Each data set comprises a plurality of forms of at least one biological state class, with a plurality of data points (samples) belonging to each of the forms of the class…
>
> Data sets are independent of each other to reduce collection bias in ultimate classifier selection. For example, they can be collected from multiple sources and may be collected at different times and from different locations using different exclusion or inclusion criteria, i.e., the data sets may be relatively heterogeneous when considering characteristics outside of the characteristic defining the biological state class.

The subject data from each subject comprises measurements of a plurality of data elements from each subject sample. As taught on page 24, of the disclosure, Applicants describe data elements in the method, where **each independent data set of samples comprises separate data elements**:

> Data elements are features of a data point representing characteristics of the data point. For example, in one aspect, data elements represent expression values of a plurality of different genes in a sample from a patient having a disease

> shared in common among patients contributing samples to the data set. Each data set comprising data points I through i, will have at least two classes of data points representing at least two forms of a biological state class, present in the sample source providing the data point (class +1) or absent in the sample source providing the data point (class -1). In one aspect, the class -1 data point represents a control (e.g., negative for a disease), though this is not necessarily so.

Applicants teach generation of the two independent data sets on p. 30, where:

> Thus, for example, the biological state class might be a particular kind of cancer, and the forms of that class might be presence or absence of that cancer. The data points might represents blood samples from individuals who fall into one of the two forms of the class, that is having cancer or cancer free. Data elements are then generated for each data point by analysis of the sample. For example, the samples might be analyzed by gene expression array technology to determine the expression of any number genes. Alternatively, the samples might be analyzed by protein expression profiling, such as SELDI, to determine the expression of any number of proteins, e.g., in the form of mass spectrometry peaks. In each case, each gene or protein is a data element, and the value of each data element is, respectively, the level of expression as measured by the particular technology. **The results of this analysis will be two independent data sets populated by the samples in each data set and further characterized by expression levels of the plurality of genes or proteins in each sample**. The data might be presented in the form of two data arrays in form of rows and columns: **Each array would contain data from a different data set; each row would represent a sample (data point); each column would represent a gene or protein (data element) and each cell would represent the level of expression of the gene or protein (data element value)**. (emphasis added).

Accordingly, the results from separately and independently conducted analyses are cross-compared to identify a subset of potential biomarkers that share a comparable level of performance on data from each individual source and share the same up/down regulation patterns between the different groups of samples across the multiple sources of data. For example, on p.44 – 45, Applicants teach selecting an

initial subset of data elements from each of the data sets, followed by selecting the intersecting subset:

> A subset of data elements, e.g., genes or proteins, is now selected from each data set based on selection criteria. Generally, the genes or proteins that are the "best" classifiers from each data set will be selected. For example, the selection criteria might be to "top ten percent" or "the genes or proteins that provide a specified level of sensitivity and/or specificity." All the data elements from each data set that meet the selection criteria are selected for initial subsets. For example, if there are one hundred genes or proteins that have been ranked in each data set, the top ten percent or discriminators, or ten genes or proteins each, might be selected for the initial data sets.:
>
> Most often, these initial subsets will not be identical in terms of the data elements that populate them. However, if they contain data elements in common, these data elements can be selected into an intersection subset. So, for example the initial subset from data set 1 might contain genes or proteins 1, 3, 5, 7 and 9. The initial subset from data set number 2 might contain genes or proteins 1, 2, 3, 4 and 5. The intersection subset could contain any or all of genes or proteins 1, 3 and 5, as the data elements common to both initial subsets.
>
> More specifically, the results from the plurality of data sets are cross-compared to determine a final set of common data elements with consistent expression patterns as a panel of potential biomarkers. Thus, data elements which are selected or qualified as having good "values" or "weights" using the learning algorithms described above in independent discovery data sets are compared, to select an intersection subset of data elements, wherein the data elements in the intersection subset are those which have good values for a plurality of data sets, i.e., the data elements are consistently good biomarkers. Although ideally, a "good value" refers to a data element which has greater than at least 80% specificity and greater than at least about 70% sensitivity in tests to detect or diagnose the biological state class.

In contrast, the Petrocoin reference is directed to the generation of proteomic spectra from serum to identify proteomic patterns that distinguish neoplastic from non-neoplastic disease in the ovary. As pointed out by the Examiner, the Petrocoin reference teaches only teaches two biological state classes- "unaffected women" and "women with ovarian cancer" (see, e.g. table 2, p.576). The Petrocoin reference uses an iterative searching algorithm to identify a proteomic pattern to discriminate cancer from non-cancer, and then apply that pattern to classify independent sets of samples (see Figure 1). This is in contrast to the present invention, where **two independent data sets** are populated by the samples in each data set and further characterized by expression levels of the plurality of genes or proteins in each sample, and then the results from the separate analyses are cross-compared to identify a subset of potential biomarkers.

Clearly, the data sets taught by the instant application and the data sets taught by the Petrocoin reference are different.

Applicants direct the Examiner to page 17 of the disclosure where "intersection subset" is defined:

> "Intersection subset" refers to subset of common data elements in a plurality of independent discovery data sets which have been identified independently in each data set as meeting the selection criteria for each independent data set; i.e., in one aspect, a data element in an intersection subset is identified as highly discriminatory (greater than at least 80% specificity and greater than at least about 70% sensitivity in tests to detect or diagnose the biological state class) in each of the independent discovery data sets.

Neither Petricoin nor any of the other cited documents disclose or suggest use of an intersection subset of data elements as Applicants disclose and claim.

Golub fails to remedy such deficiencies of the Petricoin document. The Golub reference is directed to identifying new cancer classes (class discovery) or for assigning tumors to known classes (class prediction). Golub use an initial sample, ALL and AML to create a class predictor to classify new, unknown samples. Golub use a fixed subset of informative genes to make a prediction on the basis of expression level of these

genes in a new sample. (see Fig 1B). The approach was tested on 38 leukemia samples with a set of 50 genes-predictors that were derived in cross-validation tests, and assigned the samples as AML or ALL. (see p. 523, third column). Nowhere does Golub disclose or suggest using subsets of the original data sets to select an intersection subset.

Barnhill also does not disclose or suggest use of first and second independent discovery data sets as Applicants claim. Barnhill also does not suggest disclose or suggest using subsets of the original data sets to select an intersection subset.

Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the foregoing rejections.

CONCLUSION

In view of the above amendment and response, Applicants believe that the pending application is in condition for allowance.

The Director is hereby authorized to charge any credits or deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 04-1105, under Order No. 58369 (71699).

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Respectfully submitted,

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